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Citation for final published version:

Stamoulis, Catherine, Vanderwert, Ross ORCID: <https://orcid.org/0000-0002-2280-8401>, Zeanah, Charles H., Fox, Nathan A. and Nelson, Charles A. 2017. Neuronal networks in the developing brain are adversely modulated by early psychosocial neglect. *Journal of Neurophysiology* , jn.00014.2017. 10.1152/jn.00014.2017 file

Publishers page: <http://dx.doi.org/10.1152/jn.00014.2017>
<<http://dx.doi.org/10.1152/jn.00014.2017>>

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Neuronal networks in the developing brain are adversely modulated by early psychosocial neglect

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Running title: Effects of early psychosocial neglect on brain networks

25 **Abstract**

26

27 The brain's neural circuitry plays a ubiquitous role across domains in cognitive processing and undergoes
28 extensive re-organization during the course of development in part as a result of experience. In this paper we
29 investigated the effects of profound early psychosocial neglect associated with institutional rearing on the
30 development of task-independent brain networks, estimated from longitudinally acquired
31 electroencephalographic (EEG) data from <30 to 96 months, in three cohorts of children from the Bucharest
32 Early Intervention Project (BEIP), including abandoned children reared in institutions who were randomly
33 assigned either to a foster care intervention or to remain in care as usual and never institutionalized children.
34

35 Two aberrantly connected brain networks were identified in children that had been reared in institutions: 1) a
36 hyper-connected parieto-occipital network, which included cortical hubs and connections that may partially
37 overlap with default-mode network and 2) a hypo-connected network between left temporal and distributed
38 bilateral regions, both of which were aberrantly connected across neural oscillations. This study provides the
39 first evidence of the adverse effects of early psychosocial neglect on the wiring of the developing brain. Given
40 these networks' potentially significant role in various cognitive processes, including memory, learning, social
41 communication and language, these findings suggest that institutionalization in early life may profoundly
42 impact the neural correlates underlying multiple cognitive domains, in ways that may not be fully reversible in
43 the short term.

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49 **New and noteworthy**

50 This paper provides first evidence that early psychosocial neglect associated with institutional rearing
51 profoundly affects the development of the brain's neural circuitry. Using longitudinally-acquired
52 electrophysiological data from the Bucharest Early Intervention Project (BEIP), the paper identifies multiple
53 task-independent networks that are abnormally connected (hyper- or hypo-connected) in children reared in
54 institutions compared to never-institutionalized children. These networks involve spatially distributed brain
55 areas and their abnormal connections may adversely impact neural information processing across cognitive
56 domains.

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59 **Keywords:** Brain networks, EEG, early development, psychosocial neglect

60 **Introduction**

61 From the microscale of individual neurons to the macroscale of cortical regions, the brain's neuroarchitecture
62 is characterized by networks organized into topologies that ensure flexible, rapid and efficient neural
63 information processing (Bullmore & Sporns, 2009). These networks may be divided into two broad categories:
64 task-related networks that are activated and coordinated in response to cognitive demands and external stimuli,
65 and task-independent (resting-state or stimulus-independent) networks that are spontaneously active and
66 coordinated when the brain is not actively engaged in specific cognitive tasks. In some cases, task-dependent
67 networks increase their activity and coordination at the same time as specific task-independent networks
68 decrease theirs (Fox et al., 2005). Thus, in part due to these inverse correlations, task-independent networks
69 may play a critical role in cognitive function and neural information processing (Raichle et al., 2001, 2007;
70 Dosenbach et al., 2008; Kelly et al., 2008). Predominantly fMRI studies in adults have identified several
71 distinct, and in some cases inter-connected task-independent networks, including the default-mode network
72 (DMN) (Greicius et al., 2003; Vincent et al., 2006; Mantini et al., 2007; Ward et al., 2014). The topologies of
73 these networks, estimated from fMRI data with excellent spatial resolution, may be directly correlated with
74 those of structural networks (Greicius et al., 2009; Barttfelt et al., 2015). Previous studies have associated
75 disrupted task-independent networks, with neuropsychiatric disorders, including schizophrenia and autism
76 (Kennedy et al., 2006, Bluhm et al., 2007).

77

78 The dynamic evolution of task-independent networks in the developing brain is poorly understood and our
79 current knowledge is primarily based on fMRI studies. Elements of these networks come on line early in
80 infancy (Fransson et al., 2007), but at least the DMN, which includes the ventral medial prefrontal cortex,
81 anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), lateral temporal cortex, precuneus and
82 lateral parietal inferior gyri and the hippocampal formation (Greicius et al., 2003; Buckner et al., 2008), may
83 be incompletely connected even at ages 7-9 years (Fair et al., 2008). Negative early experiences and stressors,

84 including poverty, abuse and psychosocial neglect, may have profound effects on neural maturation and
85 consequently brain structure and function. In fact, social and emotional deprivation associated with
86 institutional rearing has been shown to adversely affect brain's structure (Eluvathingal et al., 2006; Bauer et
87 al., 2009; Sheridan et al., 2012; Bick et al., 2015), metabolism (Chugani et al., 2001; Tottenham et al., 2011)
88 and electrical activity (Marshall et al., 2004, 2008; Vanderwert et al., 2010; McLaughlin et al., 2010, 2011;
89 Stamoulis et al., 2015). Earlier work on the Bucharest Early Intervention Project (BEIP), a longitudinal study
90 of children with a history of severe early deprivation (see Zeanah et al., 2003; Nelson et al., 2014), has shown
91 that early psychosocial deprivation significantly impacts age-related dynamics in the developing brain's
92 rhythms (Stamoulis et al., 2015). In the same sample, Marshall et al. (2008) showed that removal from an
93 institution and placement in a foster care home prior to 24 months of age resulted in higher local network
94 synchrony and statistically higher power in the alpha band (8-12 Hz) in the first 4 years of life in comparison
95 to children who remained in institutions. A positive modulatory effect of foster care placement was also
96 reported in other oscillations (Stamoulis et al., 2015), although changes in these oscillations from 42 to 96
97 months were found to be distinct in children removed from institutions and placed in foster care compared to
98 those who had never been institutionalized. These results highlight the profound adverse effects of early
99 institutionalization on the developing brain.

100

101 There are very few studies that have investigated task-independent networks in the developing brain and no
102 previous work on the effects of neglect on these networks. This study investigated the topologies of task-
103 independent networks and their developmental trajectories in children participating in the BEIP. Longitudinal
104 electrophysiological (EEG) data from 3 cohorts were analyzed, including a group of institutionalized children
105 who were randomized to a high-quality foster care placement (the foster care group), a group randomized to
106 remain in institutional care (care as usual group) and a group of children who had never been institutionalized
107 and lived with their families in the Bucharest community (never institutionalized group). Although EEG has

excellent temporal resolution, it lacks the high spatial resolution of fMRI and cannot resolve network topologies with the same spatial specificity as fMRI. Consequently, brain network topologies estimated from fMRI (which measures hemodynamic responses) and EEG (which measures neural activity) are not directly comparable. Nevertheless, EEG may still provide spatially sparse connectivity information on task-independent networks that may overlap with those identified by fMRI. Here we hypothesized that the spatial organization, properties and age-related dynamics of these networks are significantly impacted by early neglect in a frequency-specific manner, resulting in aberrant topologies that impair the efficiency of neural information processing and consequently cognitive function.

Materials and Methods

1. Bucharest Early Intervention Project (BEIP)

The BEIP is an ongoing longitudinal study that started in 2001 as a randomized controlled trial with foster care as an intervention for young children who had been abandoned at birth and placed in institutions. Using multi-modal data, the study aims to investigate the effects of early psychosocial deprivation on the structure and function of the developing brain and potentially beneficial effects of removal from an institution and foster care placement (Zeanah et al, 2003, Nelson et al, 2014). One hundred thirty-six children who had been reared in institutions entered the trial at ages 6-30 months, and were randomized to two arms, care as usual (CAUG; $n = 68$), i.e., more prolonged institutional rearing and foster care (FCG; $n = 68$), i.e., placement in high-quality foster care specifically created for the project. A comparison group of 72 Romanian children who had never been institutionalized and lived with their families in Bucharest communities were also recruited (NIG).

2. Participants

The present study sought to quantify the age-related changes in task-independent networks using longitudinally acquired EEG signals from the BEIP cohorts, with an emphasis on 42 and 96 months (although

data at all ages were analyzed). Thus, only subgroups of the BEIP cohorts with measurements at a minimum of 2 time points were included. Also, 4 children in the CAUG with diagnosed Autism Spectrum Disorder (ASD) were excluded. The characteristics of these groups are described in more detail in (Stamoulis et al., 2015). Sixty-two children in the CAUG (median age at study entry = 23.0 months, inter-quartile range (IQR) = 9 months), 61 children in the FCG (median age at study entry = 23.0 months, IQR = 11 months), and 44 children in the NIG (median age at study entry = 21.5 months, IQR = 12 months) were studied.

3. Demographic data

Age, which varied between participants both at study entry and the second assessment (30-33 months) but not at 42 or 96 months, gender, age at foster care placement for children in the FCG, percent time spent in institutions for children in the FGC and CAUG, birth weight and head circumference were included in the analysis as potential covariates. All missing data were assumed to be missing at random, mainly as a result of longitudinal attrition. Eighty-four females and 83 males were studied. Birth weight varied in the range 0.9 – 4.5 kg (median = 3.0 kg, IQR = 0.8 kg). These data were missing in 15 children. There were no statistically significant differences in birth weight between the CAUG and FCG (median of CAUG = 2.8 kg, median of FCG = 2.6 kg, $p = 0.14$) but both groups had statistically lower birth weights than the NIG (median of NIG = 3.3 kg, $p < 0.001$). Head circumference was measured at all 4 time points. These data were missing for 17 children at baseline, 16 at 30 months, 25 at 42 months and 32 at 96 months. Median circumference at baseline was 46.8 cm, IQR = 2.5 cm, 48.0 cm at 30 months IQR = 2.0 cm, 48.6 cm at 42 months, IQR = 1.6 cm, and 51.0 cm at 96 months, IQR = 2 cm. There were no significant differences in head circumference between the CAUG and FCG at any age ($p = 0.18$ at baseline, $p = 0.07$ at 30 months, $p = 0.09$ at 42 months, $p = 0.38$ at 96 months). In the FCG, age at foster care placement was in the range 6.8 – 33 months, median = 24.8 months, IQR = 10.1 months. Time spent at institutions at baseline, 42 and 96 months is summarized in Table S1.

4. EEG data characteristics and pre-processing

EEGs were collected at study entry (baseline) as well as at 30-33, 42 and 96 months, using an Electro-Cap (Electro-Cap International Inc) system (12 scalp electrodes: F3, F4, Fz, C3, C4, P3, P4, Pz, T7, T8, O1, O2). The characteristics of these data are described in detail in (Marshall et al, 2008, Vanderwert et al, 2010, Stamoulis et al, 2015). At baseline, 30-33 months and 42 month assessments, task-independent EEG signals were recorded while lights were turned off for ~1-3 min. At 96 months, task-independent EEG signals were recorded during 1-min intervals of eyes-closed (EC) and eyes-open (EO). Only signals recorded under the EC condition were included in the analysis. Data were sampled at 512 samples/s and bandpass filtered during acquisition in the range 0.1- 100 Hz. Prior to analysis all signals were referenced to an average reference. Previous work has shown that in the absence of appropriate source modeling, which is difficult with a small number of electrodes, an average reference results in substantially lower connectivity errors than a mastoid or Cz reference (Chella et al, 2016). However, similar to all referencing approaches, an average reference has shortcomings, too, particularly for localizing specific EEG waveforms such as event-related potentials (ERP). Here, the issue of localization is of less concern. Also, several studies have shown that for connectivity analyses, even with a low number of EEG electrodes average referencing is preferable to the use of a common reference (Dien, 1998). A stopband filterbank of 3rd order elliptical filters with a 1-Hz bandwidth, 0.5 dB ripple in the passband and 20 dB in the stopband was used to suppress the power line noise at 50 Hz and its 100-Hz harmonic. Artifacts associated with eye blinking were locally suppressed using a matched-filtering approach, where signal templates for eye blinks were used to detect intervals containing these artifacts (Stamoulis et al., 2009). Individual EEG signals were further denoised via signal decomposition and elimination of random components identified based on their autocorrelation function (Stamoulis et al., 2014). Finally, signals containing extreme amplitude outliers, i.e., above a threshold equal to the median plus 3 times the inter-quartile difference (Tukey, 1977) were also eliminated. These outliers are likely to be associated with broadband muscle and/or other non-neural activity. Consequently, 1-s intervals containing outliers were

excluded from the signal decomposition and mutual information estimations.

5. Signal analysis

5a. Estimation of narrowband EEG signal components (individual oscillations): Neural oscillations in the developing brain may have characteristic frequencies that do not fall within the limits of traditional biological bands (delta to ripple), established based on adult brain signals. Thus, frequency domain analysis of bandpass filtered signals in these bands may not be appropriate. Instead, a fully unsupervised, time-domain approach based on the Ensemble Empirical Mode Decomposition method (EEMD, Wu et al, 2005) was used to estimate neural oscillations and their dominant frequencies. The EEMD is a modification of the classical EMD method (Huang et al, 1998) and accounts of the problem of mode (component) mixing. The estimation process has been described in detail in previous work (Stamoulis et al., 2015). Task-independent network connectivity was estimated for individual oscillations of the EEG to construct frequency-specific networks. Briefly, each EEG signal was decomposed into a small set of narrowband components that significantly contributed to the broadband signal amplitude. The cost function proposed in (Stamoulis et al, 2011) was also used to select non-random components and eliminate noise-related signal contributions with substantial amplitude. A sliding 1-s window was used in all estimations. In exploratory analyses of the data, the window length was varied between 1 and 4 s, yielding similar estimates in oscillation amplitude, frequency and connectivity.

Glossary of terms: The following network parameters were estimated for each identified oscillation in the EEG: a) *spatially averaged connectivity* (over the entire brain and over individual networks identified in models to be statistically distinct between groups), b) non-directional *edge-specific connectivity* for each edge connecting pair of network nodes and c) *node centrality*, a measure of the importance of each node in the network. Each electrode was treated as a network node. Spatially-averaged and edge-specific connectivities were quantified using *mutual information*, an information theoretic measure (see 5b). Two types of

connectivity matrices were estimated for each child at each time point and each oscillation, a weighted connectivity matrix containing the actual mutual information values and thus the actual connection strengths between pairs of nodes and the adjacency matrix, a binary matrix of edge connection/non-connection obtained by appropriately thresholding the weighted connectivity matrix. Based on connectivity thresholds two sets of networks were identified, hyper- and hypo-connected networks (see 5c and 5d). Node centrality was quantified using node strength, a measure of the sum of its connections based the adjacency matrix (see 5e).

5b. Estimation of oscillation-specific connectivity: In the case of a large number of electrodes, connectivity analysis may be best conducted at the source level, to appropriately address issues of volume conduction which may impact various connectivity measures. The adequacy and accuracy of source connectivity analysis in the case of 12 electrodes are questionable, independently of the source separation or localization methods used. Information-based connectivity measures have been shown to be relatively robust to volume conduction (Vicente et al, 2011) and were used in this electrode-level analysis. Mutual information was used to quantify undirected pairwise network connectivity. Together with other information theoretic measures, it has been previously used in a number of studies to quantify correlation between electrophysiological signals and may be more robust to the inherent noise of these signals than other measures such as coherence (Vejmelka et al, 2008; Schreiber, 2000; Palus et al, 2001; Stamoulis et al, 2013). Mutual information $I(X, Y) = \sum_{x,y} p(x, y) \log \frac{p(x, y)}{p(x)p(y)} \geq 0$, between random variables X and Y measures their mutual dependence (Cover & Thomas, 2004). It is a function of their joint and marginal probability density functions $p(x, y)$, $p(x)$ and $p(y)$, which were estimated using a kernel-based method (assuming a Gaussian kernel) following segmentation of EEG signals in 1-s windows. Across ages and participants, a kernel bandwidth of 0.8 was used in the estimation and the probability density functions were evaluated at 200 points.

5c. Connectivity threshold estimation: Edge-specific mutual information thresholds were estimated as

228 follows: for each oscillation and network edge, the median (across subjects) mutual information for the NIG
 229 (and thus each age-matched oscillation and edges in the control group) was calculated as well as
 230 corresponding 95% confidence intervals (CI), using bootstrapping with replacement (2000 draws and an
 231 accelerated, bias-corrected percentile method (Efron, 1993)). The edge-specific upper CI for the NIG median
 232 mutual information was selected as an edge's threshold for edge hyper-connectivity, and the corresponding
 233 lower CI was selected as the threshold for edge hypo-connectivity.

234

235 **5d. Adjacency matrix estimation for relative hyper- and hypo-connectivity:** Based on the above
 236 thresholds, two sets of adjacency matrices - with elements (i, j) for edges connecting nodes i and j , for each
 237 oscillation-specific undirected graph were estimated for the CAUG and FCG, 1) the *hyper-connectivity*
 238 *adjacency matrices*, with elements that were equal to 1 for edges that exceeded the upper CI for median
 239 connectivity of the NIG and zeros elsewhere, 2) the *hypo-connectivity adjacency matrices*, with elements that
 240 were equal to 1 for edges that were below the lower CI for median connectivity of the NIG and 0 elsewhere.

241

242 **5e. Estimation of node centrality:** The maximum number of possible connections of each node in the
 243 estimated networks is 12 (a self-connection and 11 connections to all other nodes). There are several ways to
 244 define *node centrality*, i.e., the importance of a node in a network. Here it is defined in two ways: 1) in terms
 245 of *node strength*, i.e. the ratio of the sum of all edge weights for a node over the maximum possible sum of

246 weights, so for node $c_i = \frac{\sum_j I_{ij}}{\max \sum_j I_{ij}}$; 2) in terms of *node connectedness*, i.e., the ratio of the sum of all

247 binary edge values for a node over the maximum possible sum of weights i.e., $c_i = \frac{\sum_j A_{ij}}{\max \sum_j A_{ij}}$. Based on
 248 these topological measures it is possible to identify potential *hubs*, i.e., highly connected nodes that are critical
 249 for information processing through the network. Note that the adjacency matrices for the CAUG and FCG

were estimated as described in sub-section 5d. The adjacency matrices for subjects in the NIG were estimated assuming the median (across subjects and electrodes) MI as the corresponding connectivity threshold.

6. Statistical analysis

Differences in network characteristics at individual ages were assessed using ordinary linear regression models, with edge connectivity or node centrality as the dependent variable, and group (using criterion coding to avoid including several group variables given the relatively small sample), time spent in institutions, birth weight, head circumference, age at foster care placement and gender (categorized as female = 0, male = 1) as independent variables. In these models (as well as in mixed effects models used to assess age-related parameter changes), each edge or node parameter were assessed independently, i.e., nodes/edges were not compared to each other. Instead, their individual (independent) correlation with the predictors and confounders were assessed. Therefore, corrections for multiple comparisons were not necessary, particularly in mixed effects models (Gelman et al, 2012). Combinations of independent variables were included in separate models. Logistic regression models with group as the dependent variable (assuming the NIG as the reference category) and network measures as independent variables were also developed. Finally, in cases where network parameters were found to be statistically distinct among the 3 groups, their relationship was also investigated through logistic regression models that included only the CAUG (= 0) and FCG (= 1), i.e., the groups in the two arms of the randomized trial. All modeling approaches yielded consistent results. Note that at baseline (prior to the randomization) there were only two groups, institutionalized and never-institutionalized.

Linear mixed effects models were developed to investigate temporal trajectories of network characteristics. For all children randomized to the intervention arm, foster care placement occurred before 42 months of age. Therefore, to assess intervention-related effects we focused on changes in network parameters between 42 and 96 months. Thus, the models included a subject-specific intercept and a subject-specific age slope, to account

for potential subject-specific variabilities. Independent variables included gender, birth weight, head circumference, group, age at foster care placement and percent time spent at institutions. Given the sample size, only relatively small models were developed with combinations of 1-3 independent variables. All analyses were done using the software Matlab (Mathworks, Inc, Natick MA, USA).

Results

We investigated oscillation-specific network properties at all 4 age assessments, and their developmental changes from 42 to 96 months. We first examined spatially-averaged (global) connectivity followed by edge-specific connectivity and node centrality. We conducted two complementary analyses: 1) Using connectivity thresholds derived from the NIG, we compared the FCG and the CAUG relative to NIG. We thus present results on abnormal networks in the FCG and CAUG that were found to be *hyper-connected* or *hypo-connected* relative to the NIG; 2) We compared all 3 groups to each other via statistical models that included adjustments for birth weight or head circumference. We report network measures only for subnetworks that were found to be statistically distinct in the 3 groups. As previously noted, regression models were also developed to compare only the CAUG and FCG, separately from the NIG. Statistically significant group differences in network parameters identified in these models were consistent with those identified using models that included the NIG.

1. Brain-wide (spatially-averaged) connectivity

First, median (over electrodes) mutual information (MI) that had been averaged in time was compared between groups for each estimated oscillation at each assessment age, to assess potential differences in brain/hemisphere-wide connectivity. Corresponding frequency-connectivity relationships at these ages (unadjusted for confounders or other covariates) are shown in Figure 1. Inter-quartile ranges (vertical bars for MI and horizontal bars for frequency) are shown. In these unadjusted connectivity data, no significant

298 differences were found between groups except for the gamma oscillation at 96 months ($p = 0.012$), and the
 299 alpha and theta oscillations at baseline (study entry) ($p = 0.002$ and $p = 0.016$ for alpha and theta connectivity
 300 respectively). When adjusted for birth weight or head circumference, significant differences in whole brain
 301 and hemisphere-specific connectivity were estimated between institutionalized and never institutionalized
 302 children in the theta band at baseline ($p = 0.006$ for the entire brain, $p = 0.002$ for the left-hemisphere and $p =$
 303 0.034 for the right hemisphere). When adjusted for age at foster care placement, significant group differences
 304 in left-hemisphere theta connectivity were estimated at 96 months ($p = 0.035$). When adjusted for head
 305 circumference, significant group differences in beta connectivity were also estimated in the left hemisphere at
 306 96 months ($p = 0.044$). The statistics of oscillation frequencies at each assessment age are summarized in
 307 Table S1.

308

309 **2. Network topologies at 4 assessment ages**

310 All reported connectivity parameters in the CAUG and FCG are relative to the corresponding NIG parameters.
 311 For each assessment age and oscillation, network topologies for the two groups are shown in Figure 2. Note
 312 that these connectivities are unadjusted for potential confounders and are solely based on thresholding of the
 313 MI matrices. Appropriate adjustments were included in the analysis and are described in the next section. For
 314 each oscillation, topologically distinct hyper- and hypo-connected subnetworks were identified in the CAUG
 315 and FCG with some overlap of their elements across oscillations. At baseline, both groups had a large number
 316 of hyper-connected edges (up to $\sim 85\%$ of all possible edges) and a small number of hypo-connected edges.
 317 This number decreased significantly from baseline to the second assessment (from more than 75% to $\sim 25\%$ of
 318 all possible connections), potentially due to neural maturation and elimination of redundant connections. No
 319 substantial topological differences were estimated between the two groups at those ages. At 42 months, an
 320 even lower number of hyper-connected edges were identified in both groups, asymmetrically clustered in the
 321 left hemisphere and primarily in temporo-parietal and parieto-occipital regions in the gamma and beta

networks, but less consistently (in space) in other networks. For some oscillations, a small number of hypo-connected edges were also identified. Finally, at 96 months, more consistent topologies were identified in both groups: a) a hyper-connected gamma network with aberrant connections between bilateral parietal and occipital regions; b) relatively larger hypo-connected beta and alpha networks with aberrant connections primarily between left and right temporal regions, left temporal and bilateral frontal and occipital regions.

3. Network topologies and parameters at 42 and 96 months

To validate the findings of the above threshold-based analysis and include appropriate adjustments for potential confounders, all 3 groups were explicitly compared at 42 and 96 months using statistical models. Statistically distinct networks based on the models are shown in Figure 3. No significant gender effects were found in any parameter at any age ($p \geq 0.40$).

3a. Network connectivity

i) Forty-two months: Although the above threshold-based analysis identified statistically distinct edges between the NIG and both the CAUG and FCG, when adjusted for birth weight or head circumference at that age in the models, no statistically distinct edges were identified between the 3 groups. The effect of age at foster care placement was found to be significant for right fronto-central (F4, C4) and centro-parietal (C4, P4) regions in the gamma networks, with statistically higher connections in the CAUG followed by the FCG and the NIG ($p = 0.007$, Wald statistic = 7.74 for group, $p = 0.006$, Wald statistic = 7.63 for age at foster care placement). Connectivity between occipital regions was also statistically higher in the CAUG followed by the FCG and the NIG and in the alpha and theta networks ($p = 0.013$, Wald statistic = 6.39 for group, $p = 0.027$, Wald statistic = 5.04 for age at foster care placement in the alpha network, and $p = 0.030$, Wald statistic = 4.87 for group, $p = 0.047$, Wald statistic = 4.07 for foster care placement in the theta network).

346 **ii) Ninety-six months:** The majority of aberrantly connected edges identified by the threshold-based analysis
347 were also found to be distinct in the 3 groups through the statistical models. For oscillations in the gamma to
348 theta ranges, statistically distinct sub-networks/edges and corresponding brain regions are summarized in
349 Table 1. Related model statistics for these edges and sub-networks are summarized in Table S3. Adjustments
350 for birth weight and age at foster care placement were non-significant in all models ($p > 0.17$ for birth weight
351 and $p > 0.06$ for age at placement). Similarly, the adjustment for head circumference was non-significant for all
352 models for gamma connectivity ($p > 0.2$), all models for beta connectivity with the exception of the (F3, T7)
353 connectivity ($p = 0.047$) and marginally for the (F4, T7) connectivity ($p = 0.056$), all models for alpha
354 connectivity with the exception of the (P3, Pz), (P4, Pz) and (T7, O2) connectivities ($p = 0.028$, $p = 0.019$ and
355 $p = 0.030$ respectively), and all models for theta with the exception of the (P3, P4) connectivity ($p = 0.020$ for
356 theta). Median mutual information for each group is shown in column 2.

357

358 Within the gamma network, the parieto-occipital sub-network (P3, Pz, P4, O1, O2 and averaged connectivity
359 in this subnetwork) was found to be statistically distinct in the 3 groups with highest connectivity in the
360 CAUG followed by FCG. Elements of this subnetwork were also hyper-connected across frequency ranges.
361 In the beta network, the left temporal region (T7) in the CAUG and FCG was statistically hypo-connected to
362 several other brain regions, including bilateral frontal (F3, Fz, F4), right temporal (T8), bilateral parietal (P3,
363 Pz, P4), bilateral occipital (O1, O2) and right central (C4). These connectivities, as well as averaged
364 connectivity in the corresponding subnetwork were distinct in the 3 groups, with statistically lowest values in
365 the CAUG. We examined the raw signal from electrode T7 across subjects to ensure that the observed
366 laterality of these aberrant connectivities was not associated with artifacts or noise. No significant signal
367 variance differences were found between groups or subjects. All hypo-connections from the beta network were
368 also found to be distinct between groups in the alpha network, with the exception of bilateral frontal, bilateral
369 temporal and the right central – left temporal connections. Averaged connectivity in this subnetwork was also

found to be statistically lowest in the CAUG. In the theta network, fronto-parietal (Fz, Pz), bilateral centro-parietal (C3, P3) and (C4, P4), and most edges of the aberrant gamma subnetwork were statistically distinct between groups, with highest connectivities in the CAUG followed by the FCG. Also, elements of the hypo-connected beta subnetwork were distinct in the 3 groups, with lowest connectivities in the CAUG. Finally, centro-parietal connections in the theta network were also found to be statistically distinct between groups in the delta network, with highest connectivities in the CAUG.

376

377 **3b. Node centrality**

378 A few nodes with statistically distinct connectedness across the 3 groups were found both at 42 and 96 months
379 and are summarized in Tables 1 (96 months) and S4 (both ages). At 42 months, these included T7 in the
380 gamma network; Fz, T7 and T8 in the beta network; Pz in the alpha network; and Fz and Pz in the theta
381 network. At 96 months, Pz had the highest connectedness in all networks except delta, similarly for C3, C4
382 and P4 but only in the beta and alpha networks and Fz in the theta network. T7 had the lowest connectedness
383 in the beta and alpha networks. We examined the raw signals in electrode Pz across subjects to ensure that
384 increased connectedness was not due to spurious correlations between signals. No significant signal
385 differences were found between this and other electrodes. Birth weight, head circumference and age at foster
386 care placement all had a non-significant effects ($p > 0.08$ for birth weight, $p > 0.13$ for head circumference and
387 $p > 0.05$ for age at foster care placement).

388

389 A subset of nodes with distinct connectedness among groups also had distinct node strengths but only at 96
390 months. The statistics of corresponding models are summarized in Table S5. Similarly to connectedness, node
391 Pz had statistically higher strength in the CAUG in the gamma, beta and alpha networks and node T7 the
392 lowest strength in the beta to delta networks. Nodes F3, F4, Fz, and T7 all had the lowest strengths in the
393 CAUG followed by the FCG in the beta network. Finally, P4 was also found to have statistically distinct

strength in the 3 groups both in the alpha and theta networks, with highest strength in the CAUG. Birth weight and age at foster care placement had non-significant effects in all networks and nodes ($p \geq 0.09$ for both), and head circumference also had a non-significant effect ($p \geq 0.08$) except for node P4 in the alpha network ($p = 0.016$). The spatial distribution of all nodes with distinct strengths in gamma, beta, alpha and theta networks is shown in Figure 4. In addition to edges that were distinct between groups (those of Figure 3), edges that exceeded the median (over subjects) NIG connectivity but were not significantly different between groups are also superimposed (dashed lines). Independently of significance, a higher number of connections were estimated in the CAUG followed by FCG across oscillations. In summary, a few nodes in previously identified distinct subnetworks among groups were found to be either aberrant hubs or to have abnormally low centrality in the CAUG and FCG, suggesting additional topological differences between these groups.

4. Network parameter trajectories from 42 to 96 months

All previous analyses investigated network properties at individual assessment ages. To assess the impact of early neglect on the development of these networks, we also investigated the age-related changes in estimated parameters from 42 to 96 months using appropriate statistical models for repeated measures.

4a. Connectivity trajectories

For each oscillation, the changes in all network edges were estimated and compared between groups, using mixed effects regression models that included time (age), group and birth weight or head circumference (and/or age at foster care placement) as independent variables and pairwise MI as the dependent connectivity variable. The statistics of these models for edges that were distinct between groups are summarized in Table S6a. The effect of time (age) was significant in all these models ($p \leq 0.01$). Birth weight, and head circumference had non-significant effects in all models ($p > 0.17$ for birth weight, $p > 0.26$ for circumference). A small number of network connections had distinct age-related changes across groups, including (P3, Pz) and

418 (P4, O2) across oscillations except delta, and (C3, P3), (P3, O2), (P4, O1) and (Pz, O2) in the gamma network.
419 Note that with the exception of (C3, P3) these edges were also found to be distinct at 96 months and were part
420 of the parieto-occipital hyper-connected subnetwork in the CAUG and FCG compared to NIG.

421

422 **4b. Node centrality**

423 With the exception of node P3 in the gamma network with marginally significant age-related changes across
424 groups ($p = 0.053$, Wald statistic = 3.77) no other node strength changed significantly from 42 to 96 months.
425 However, connectedness in nodes P4 and Pz in the alpha and theta networks changed in a statistically distinct
426 way across groups. Both nodes belong to the subset of nodes with distinct connectedness at 96 months in the 3
427 groups (Pz also had statistically distinct connectedness at 42 months; see Table S6b). Birth weight and head
428 circumference had non-significant effects ($p > 0.21$ for birth weight, $p > 0.05$ for head circumference). These
429 results suggest that at least elements (nodes and edges) of task-independent networks develop abnormally as a
430 function of age in children reared in institutions, resulting in significant differences at 96 months.

Discussion

In this paper we report the impact of early psychosocial deprivation associated with institutionalization on the topologies and age-related dynamics of frequency (oscillation)-specific, task-independent brain networks in three groups of children from the BEIP. To investigate these topologies, we have used multiple statistical modeling approaches and network measures. Our present findings extend previous work (Stamoulis et al, 2015), which has shown that early institutionalization has profound and widespread effects on broadband neural activity.

In children reared in institutions and thus subjected to early neglect, this study has identified two aberrantly connected networks, particularly at 96 months: 1) the *aberrantly hyper-connected parieto-occipital gamma network* in the CAUG and FCG, both with statistically higher connectivity than the NIG, but also with distinctly different connectivity from each other. Elements of this subnetwork were also aberrantly hyper-connected at lower frequencies (beta, alpha and theta networks); 2) the *hypo-connected fronto-temporal network* at frequencies below the gamma range (beta to delta) in the CAUG and FCG compared to NIG at 96 months, but also distinctly different from each other. Although the adverse effects of early stressors on neural maturation and the development of human brain networks remain elusive, there is substantial evidence that brain development is significantly impacted by early experiences (Nelson et al, 2006). Therefore, negative experiences may significantly and differentially affect the maturation of the brain's neural circuitry, impairing both selective connection strengthening (leading to hypo-connected networks), and/or connection pruning (leading to networks that appear aberrantly hyper-connected at the macroscale). Both types of aberrant networks may prevent efficient neural information processing.

It is important to note the statistically lower connectivity in the FCG (although still statistically higher than NIG) compared to CAUG in the parieto-occipital network, suggesting a positive effect of the foster care

intervention in lowering aberrant hyper-connectivity. Previous work has shown that this network is synchronized in the gamma band during visual processing (Helfrich et al, 2014). Abnormally high connectivity may imply reduced flexibility of this network to modulate its activity during visual task performance. In fMRI studies, elements of this network have been previously identified as major cortical hubs (Tomasi et al., 2011). Here, parietal nodes, which may overlap with this network, were found to be aberrant hubs at multiple frequencies, with abnormally high connectivities in the CAUG and FCG compared to the NIG. These regions are involved in a wide range of cognitive processes. For example, parietal regions are often activated during episodic memory retrieval (Cabeza, et al 2008) and are involved in self-projection (Buckner et al., 2007) as well as visuo-spatial processing (Tosoni et al, 2014). Furthermore, spatial attention has been shown to modulate the coordination between parietal and occipital regions during top-down processing of spatial attention information (Lauritzen et al., 2009). Thus, abnormally high task-independent connectivity between these areas may adversely impact these cognitive processes.

Although elements of the hyper-connected parieto-occipital network had distinct connectivities in the 3 groups across frequencies, the largest number of aberrant edges in this subnetwork was estimated in the gamma frequency range. Gamma synchrony in parietal regions has been associated with visuo-motor learning and object representation (e.g., Bertrand et al., 2000; Perfetti et al., 2001; Galletti et al., 2003; Tallon-Baudry, 2009). Previous studies have shown that children reared in institutions have decreased performance on tests of visual memory and attention (Bos et al., 2009; Pollack et al, 2010; Bick et al., in press), which may be explained by decreased flexibility in the underlying neural circuitry. At lower frequencies, particularly the theta and delta ranges, fronto-parietal regions, which appeared to be aberrantly hyper-connected in the CAUG and FCG, have been shown to be part of a network that is characterized by spontaneous low-frequency activity and is anti-correlated with the DMN (Fox et al., 2005; Konrad et al., 2010), which implies that it should be weakly correlated at rest, in contrast to the DMN. Although neuronal networks identified in this study with

low spatial resolution-EEG are not directly comparable with high-resolution fMRI networks, similar anti-correlations between task-dependent and task-independent networks may be measurable by both modalities. Therefore, aberrantly high task-independent connectivity in the identified parieto-occipital network may prevent suppression of its resting activity and inhibit its functional activation.

The second major finding of this study is the *hypo-connected fronto-temporal network* at frequencies below the gamma range (beta to delta) in the CAUG and FCG compared to NIG at 96 months. Several elements of this network may overlap with previously identified task-independent networks, e.g., the resting-state auditory-phonological and visual networks reported by Mantini et al. (2007). Left middle and transverse temporal regions, covered by electrode T7, were found to be significantly hypo-connected with bilateral frontal (F3, Fz, F4), bilateral occipital (O1, O2) and right temporal (T8) regions. This node was also found to have statistically lower important (centrality) in the network in the CAUG and FCG. Left temporal regions are associated with hearing, language processing and memory. The parietal-temporal-occipital association area is responsible for integrating visual and auditory information and is involved in language comprehension. Left fronto-temporal connectivity has also been shown to be an essential network involved in syntactic processing (Tyler et al, 2011; Papoutsis et al, 2011). Note that spatially-averaged connectivity in the left hemisphere was also found to be distinct in the 3 groups at 96 months, in the beta and theta networks. Again, our findings may tap an underlying aberrant network associated with the behavioral evidence of impaired language development as a result of early institutionalization. It is important to note the distinct connectivity in this subnetwork in the CAUG and FCG, suggesting a positive effect of the foster care intervention in increasing connectivity in this subnetwork. Thus, this change could be associated with the observed improvements in language learning as a result of the foster care intervention and age of that intervention (Croft et al., 2007; Windsor et al, 2011, 2013). A previous study of structural brain connectivity in the BEIP cohort (Bick et al, 2015) has shown impaired integrity of the corpus callosum in children reared in institutions, which would in part explain lower inter-

503 hemispheric connectivity between temporal regions in the CAUG and FCG.

504

505 Although all network analyses in this study have consistently identified both the hyper-connected parieto-

506 occipital network and the hypo-connected primarily left temporal network across several frequency bands at

507 96 months, corresponding findings at 42 months were less clear. A few elements of the parieto-occipital

508 subnetwork with aberrant characteristics at 42 months remained atypically connected at 96 months, with

509 distinct properties in the 3 groups. The dynamic trajectories of part of this subnetwork were also distinct

510 among groups, potentially due to differential neural maturation rates. It is possible that additional network

511 differences were difficult to detect at 42 months due to incomplete and heterogeneous maturation of task-

512 independent networks at this age, which could make it more difficult to detect connectivity group differences.

513

514 Finally, the frequency specificity of our findings varied between networks (e.g., a larger hyper-connected

515 network in the gamma range compared to lower frequencies). Although higher-frequency networks imply

516 spatially localized processing, lower-frequency oscillations facilitate the communication (or binding) between

517 these networks. The presence of smaller numbers of aberrant connections at lower frequencies could in part be

518 due to impaired binding between high- and lower-frequency oscillations within corresponding networks. Our

519 previous work has shown decreased coupling between task-independent gamma and lower-frequency

520 oscillations, which could in part explain these findings (Stamoulis et al., 2015). Furthermore, substantial

521 topological overlap between aberrantly hypo-connected edges were observed in the alpha and beta networks.

522 Significant correlations between alpha and beta oscillations have been reported in task-independent EEGs,

523 which may explain the topological similarities between the two networks (Carlqvist et al., 2005).

524

525 Despite its many methodological strengths (including its randomized control trial design), this study is not

526 without limitations, including its relatively small sample size. Nevertheless, data from multiple time points

were included in parts of the statistical analysis, and multiple statistical models were developed to compare the cohorts, all yielding consistent results, which supports the robustness of the findings. It is, however, possible that smaller network-level differences between groups were not detectable in this sample. Second, a small number of electrodes was used to record brain activity, which prevented appropriate source-level analyses to explicitly address the issue of volume conduction. However, information-based measures of connectivity were used in this study, which have been previously been shown to be relatively robust to volume conduction. Also, the low spatial resolution of the EEG limits the estimation of detailed network topologies possible by other modalities, particularly fMRI. Despite these limitations, to the best of our knowledge, this study provides the first evidence of multiple, significantly impacted and aberrantly connected task-independent brain networks in children who have experienced severe psychosocial deprivation. Considering these networks' potential involvement in cognitive processing, including memory, visuo-motor learning, visual processing, social communication and language, these findings suggest that early psychosocial neglect associated with institutionalization may have profound adverse effects on the brain's wiring and communication, which may not be fully reversible, at least not within a few years from the intervention. Nevertheless, statistical differences between the CAUG and FCG also suggest significant positive effects of foster care on improving neural information processing facilitated by these networks.

Funding

This study was supported in part by NIH Grant R01MH091363 (Nelson) and NSF BRAIN EAGER Grant 1451480 (Stamoulis).

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Tables

Oscillation/Network	Edge Connectivity		Node Centrality	
	Hyper-connected	Hypo-connected	Highest	Lowest
Gamma-range (52.0-57.0 Hz)	<u>Regions:</u> Parietal; Parieto-occipital	—	Pz	
	<u>Edges:</u> P3-Pz; P4-O1, O2; Pz-O1,O2			
Beta-range (20.0-23.0 Hz)	<u>Regions:</u> Parietal	<u>Regions:</u> Left temporal; Bilateral frontal; Parietal; Occipital	Pz, C3, C4, P4	T7, F3, F4, Fz
	<u>Edges:</u> P3-Pz	<u>Edges:</u> T7-F3, Fz, F4, C4, P3, Pz,P4, O1, O2; F3-F4; T7-T8		
Alpha-range (8.0-10.0 Hz)	<u>Regions:</u> Parietal; Parieto-occipital	<u>Regions:</u> Left temporal; Bilateral frontal; Parietal; Occipital	Pz, C3, C4, P4	T7
	<u>Edges:</u> P3-Pz, P4-Pz, P4- O2	<u>Edges:</u> T7-F3, Fz,F4, C4, P3, Pz,P4, O1, O2		
Theta-range (3.6-4.3 Hz)	<u>Regions:</u> Midline; Centro-parietal; Parietal; Parieto-occipital	<u>Regions:</u> Left, bilateral temporal; Bilateral Centro-parietal; Parietal; Occipital	Pz, Fz, C3, C4, P4	T7
	<u>Edges:</u> Fz-Pz, C3-P3, C3-P4, O1-O2, P3-P4, P4-O1, P4-O2, P3-Pz	<u>Edges:</u> Fz-T7, Pz; C3-P3, C4-P4, P3-Pz, P4; P4-O1,O2; T7-T8; O1- O2		

Table 1: Summary of aberrantly connected and statistically distinct network elements (edges and nodes) in the three groups. For each oscillation frequency range, hyper- and hypo-connected brain regions and sets of network edges as well as aberrantly connected nodes (based on their centrality estimated either as node strength or connectedness) are listed.

Figures Legends

Figure 1: Frequency-connectivity (measured by mutual information) plots for all estimated oscillations at baseline (top left panel), and clockwise at ~30-33, 42, and 96 months respectively. At the first 3 time points connectivity was estimated from task-independent EEGs under the lights off recording condition and at 96 months under the eyes-closed condition. The 3 groups are superimposed: Care as Usual group (CAUG, red), Foster Care group (FCG, blue) and Never Institutionalized group (NIG, black). At baseline, and thus prior to randomization, children in the CAUG and FCG were part of the 'Institutionalized' group.

Figure 2: Hyper- and hypo-connected network edges and subnetworks in the CAUG and FCG relative to the NIG, for each estimated oscillation and at each assessment age (baseline to 96 months from left to right). Edges with mutual information (MI) values higher than the upper MI threshold are marked in red, and edges with MI values below the lower MI threshold are marked in green.

Figure 3: Oscillation-specific network edges for which connectivity was statistically distinct in the 3 groups, adjusted for birth weight and head circumference at each age. Left panel plots correspond to the CAUG (red), middle panels to the FCG (blue) and right panels to the NIG (black). Distinct line widths represent differential median (across the group) mutual information values, with thickest lines representing the highest median connectivity among groups and the thinnest lines representing the lowest connectivity.

Figure 4: Network nodes with aberrant strength (centrality) across groups, in the gamma, beta, alpha and theta networks. Larger circles and thicker lines reflect aberrantly and significantly higher node strength and connectivity (edge weight). Dashed lines correspond to edges above the NIG median connectivity threshold, which were not, however, statistically distinct between groups. Colors correspond to individual groups (CAUG - red, FCG - blue and NIG - black).

Supplemental Material

Assessment	Baseline		42 months		96 months	
Group	Median % time; Actual time (months)	(25 th , 75 th) quartiles	Median time; Actual time (months)	(25 th , 75 th) quartiles	Median time; Actual time (months)	(25 th , 75 th) quartiles
CAUG	98.6% 19 mo	(81.6, 100.0)% (16.9, 25.0) mo	85.0% 35.7 mo	(64.4, 97.1)% (27.0, 40.8) mo	53.0% 50.9 mo	(36.2, 79.8)% (31.2, 67.6) mo
FCG	95.9% 18.3 mo	(69.4, 100.0)% (16.3, 23.0) mo	48.9% 20.5 mo	(35.0, 61.8) % (14.7, 26.0) mo	23.40% 22.5 mo	(18.3, 28.6)% (15.0, 26.5) mo
NIG	0	0	0	0	0	0

Table S1: Summary statistics of percent time since birth spent in institutions and corresponding time in months, for each group at baseline, 42 and 96 months.

		Care as Usual Group		Foster Care Group		Never-Institutionalized Group	
Age (months)	Band range	Median (Hz)	(25 th , 75 th) quartiles	Median (Hz)	(25 th , 75 th) quartiles	Median (Hz)	(25 th , 75 th) quartiles
Baseline (< 30)	Gamma	51.82	(49.93, 53.65)	50.89	(49.71, 51.82)	49.12	(48.21, 50.35)
	Beta	20.57	(19.27, 21.30)	20.18	(19.58, 20.89)	19.82	(18.87, 20.21)
	Alpha	8.24	(7.85, 8.58)	8.23	(7.96, 8.56)	8.14	(7.87, 8.45)
	Theta	3.55	(3.42, 3.69)	3.61	(3.43, 3.70)	3.61	(3.46, 3.72)
	Delta	1.54	(1.46, 1.59)	1.56	(1.47, 1.61)	1.56	(1.50, 1.61)
30-33	Gamma	50.14	(48.41, 52.47)	51.34	(48.84, 53.69)	50.01	(48.44, 53.24)
	Beta	19.94	(18.79, 21.11)	20.47	(19.39, 21.70)	19.78	(18.55, 21.47)
	Alpha	8.20	(7.73, 8.64)	8.43	(7.92, 8.88)	8.28	(7.86, 8.82)
	Theta	3.60	(3.40, 3.79)	3.66	(3.42, 3.95)	3.64	(3.47, 3.85)
	Delta	1.54	(1.45, 1.63)	1.58	(1.49, 1.72)	1.60	(1.51, 1.64)
42	Gamma	52.96	(50.16, 55.25)	53.55	(50.59, 56.54)	53.14	(48.20, 56.59)
	Beta	20.58	(19.46, 22.01)	21.47	(19.70, 22.62)	21.34	(18.56, 22.88)
	Alpha	8.54	(8.13, 9.04)	8.69	(8.30, 9.32)	8.81	(8.17, 9.58)
	Theta	3.71	(3.56, 3.96)	3.82	(3.58, 4.14)	3.90	(3.62, 4.25)
	Delta	1.60	(1.52, 1.70)	1.65	(1.51, 1.80)	1.69	(1.56, 1.83)
96	Gamma	55.54	(53.19, 57.20)	54.34	(52.25, 55.83)	55.10	(53.26, 56.37)
	Beta	20.25	(19.43, 21.16)	20.13	(19.31, 20.86)	19.81	(18.93, 21.08)
	Alpha	8.43	(8.15, 8.76)	8.28	(8.06, 8.63)	8.45	(8.05, 8.82)
	Theta	3.67	(3.56, 3.81)	3.66	(3.53, 3.83)	3.74	(3.60, 3.90)
	Delta	1.61	(1.53, 1.66)	1.58	(1.53, 1.65)	1.61	(1.55, 1.69)

889 **Table S2:** Characteristic oscillation frequency summary statistics (medians and (25th, 75th) quartiles) for each
890 group at each assessment age.

Node pair	Median Mutual Information (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
Gamma Oscillation Connectivity						
(P3, Pz)	0.096, 0.084, 0.073	-0.009	[-0.017, -5E-04]	0.004	0.037	4.44
(P4, O1)	0.024, 0.018, 0.014	-0.005	[-0.009, -3E-04]	0.002	0.038	4.40
(P4, O2)	0.059, 0.048, 0.040	-0.009	[-0.014, -0.003]	0.003	0.002	9.66
(Pz, O1)	0.051, 0.042, 0.036	-0.006	[-0.012, -0.002]	0.003	0.008	7.27
(Pz, O2)	0.053, 0.044, 0.037	-0.007	[-0.012, -0.002]	0.003	0.007	7.58
Network	0.054, 0.048, 0.041	-0.007	[-0.011, -0.003]	0.001	0.002	9.76
Beta Oscillation Connectivity						
(F3, F4)	0.028, 0.034, 0.047	0.005	[2.00E-04, 0.009]	0.002	0.042	4.25
(F3, T7)	0.016, 0.021, 0.031	0.005	[0.002, 0.009]	0.002	0.005	8.32
(F4, T7)	0.005, 0.009, 0.013	0.003	[0.001, 0.005]	0.001	0.002	9.83
(Fz, T7)	0.006, 0.010, 0.015	0.003	[0.001, 0.005]	9.20E-004	0.002	10.02
(C4, T7)	0.003, 0.005, 0.010	0.001	[1.00E-04, 0.003]	6.30E-004	0.030	4.82
(P3, Pz)	0.115, 0.096, 0.080	-0.008	[-0.014, -0.002]	0.003	0.016	5.98
(P3, T7)	0.018, 0.027, 0.035	0.004	[4.00E-04, 0.007]	0.002	0.030	4.86
(T7, T8)	0.008, 0.012, 0.019	0.004	[0.001, 0.007]	0.001	0.004	8.60
(T7, O1)	0.010, 0.017, 0.029	0.005	[0.001, 0.009]	0.002	0.008	7.23

(T7, O2)	0.008, 0.012, 0.022	0.004	[5.00E-04, 0.007]	0.002	0.023	5.36
Network	0.012, 0.016, 0.021	0.003	[5.00E-04, 0.006]	0.001	0.021	5.44
Alpha Oscillation Connectivity						
(F3, T7)	0.038, 0.047, 0.059	0.005	[3.00E-04, 0.009]	0.002	0.036	4.50
(F4, T7)	0.022, 0.028, 0.036	0.004	[3.00E-04, 0.007]	0.002	0.031	4.78
(Fz, T7)	0.021, 0.028, 0.035	0.004	[4.00E-04, 0.007]	0.002	0.029	4.89
(P3, Pz)	0.087, 0.073, 0.063	-0.007	[-0.011, -0.002]	0.002	0.009	6.99
(P4, Pz)	0.076, 0.067, 0.057	-0.005	[-0.010, -3.0E-04]	0.002	0.036	4.52
(P4, O2)	0.070, 0.062, 0.053	-0.005	[-0.009, -0.001]	0.002	0.012	6.56
(T7, O1)	0.026, 0.040, 0.051	0.005	[9.00E-04, 0.009]	0.002	0.018	5.76
(T7, O2)	0.021, 0.027, 0.037	0.005	[0.001, 0.009]	0.002	0.013	6.37
Network	0.022, 0.029, 0.038	0.004	[7.00E-04, 0.007]	0.001	0.017	5.9
Theta Oscillation Connectivity						
(Fz, Pz)	0.011, 0.010, 0.008	-0.001	[-0.0025, -2.0E-04]	5.70E-04	0.024	5.21
(Fz, T7)	0.019, 0.022, 0.027	0.002	[2.0E-04, 0.005]	0.001	0.031	4.80
(C3, P3)	0.047, 0.041, 0.035	-0.004	[-0.008, -3.0E-04]	0.002	0.032	4.71
(C4, P4)	0.046, 0.040, 0.035	-0.003	[-0.006, -2.0E-04]	0.001	0.036	4.53
(P3, P4)	0.059, 0.053, 0.047	-0.003	[-0.006, -3.0E-04]	0.001	0.030	4.80
(P3, Pz)	0.088, 0.081, 0.073	-0.005	[-0.009, -4.0E-04]	0.002	0.032	4.73
(P4, O1)	0.051, 0.043, 0.037	-0.004	[-0.007, -7.0E-04]	0.002	0.016	5.94

(P4, O2)	0.073, 0.063, 0.056	-0.007	[-0.011, -0.002]	0.002	0.003	9.28
(T7, T8)	0.035, 0.041, 0.050	0.004	[4.0E-04, 0.008]	0.002	0.027	4.98
(O1, O2)	0.118, 0.104, 0.097	-0.006	[-0.012, -6.0E-04]	0.003	0.031	4.78
Network	0.048, 0.043, 0.040	-0.002	[0.013, -7.0E-04]	9.0E-04	0.043	4.20

Table S3: Summary of statistics for linear regression models for pairwise connectivities at 96 months as a function of group with an adjustment for birth weight or head circumference at that age. Only the statistics for pairs of nodes with statistically distinct connectivity (edge) among 3 groups are shown, as well as averaged connectivity over the subnetwork defined by these nodes/edge pairs. Median MI values for each group are provided in column 2.

Node	Median Node Centrality (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
42 MONTHS						
Gamma Oscillation Node Connectedness						
T7	0.50, 0.42, 0.17	-0.117	[-0.187, -0.047]	0.035	0.001	10.89
Beta Oscillation Node Connectedness						
Fz	0.50, 0.42, 0.33	-0.086	[-0.153, -0.019]	0.034	0.012	6.41
T7	0.67, 0.50, 0.33	-0.115	[-0.192, -0.039]	0.039	0.003	9.00
T8	0.67, 0.42, 0.17	-0.078	[-0.152, -0.004]	0.038	0.040	4.28
Alpha Oscillation Node Connectedness						
Pz	0.67, 0.50, 0.42	-0.078	[-0.143, -0.014]	0.033	0.018	5.75
Theta Oscillation Node Connectedness						
Fz	0.50, 0.33, 0.25	-0.092	[-0.152, -0.033]	0.030	0.002	9.56
Pz	0.58, 0.50, 0.42	-0.101	[-0.165, -0.037]	0.032	0.002	9.77
96 MONTHS						
Gamma Oscillation Node Connectedness						
Pz	0.50, 0.42, 0.33	-0.080	[-0.149, -0.011]	0.035	0.024	5.23
Beta Oscillation Node Connectedness						
Pz	0.58, 0.5, 0.42	-0.094	[-0.156, -0.033]	0.031	0.003	9.22
T7	0.08, 0.17, 0.25	0.079	[0.016, 0.142]	0.032	0.015	6.09

Alpha Oscillation Node Connectedness						
C3	0.50, 0.33, 0.25	-0.089	[-0.162, -0.016]	0.037	0.017	5.87
C4	0.42, 0.33, 0.17	-0.082	[-0.152, -0.013]	0.035	0.021	5.48
P4	0.50, 0.42, 0.33	-0.068	[-0.134, -0.001]	0.034	0.047	4.00
Pz	0.58, 0.42, 0.33	-0.083	[-0.147, -0.020]	0.032	0.011	6.68
T7	0.17, 0.42, 0.50	0.070	[0.001, 0.140]	0.035	0.048	3.98
Theta Oscillation Node Connectedness						
Fz	0.42, 0.33, 0.25	-0.077	[-0.135, -0.018]	0.030	0.011	6.58
C3	0.50, 0.42, 0.33	-0.085	[-0.158, -0.012]	0.037	0.022	5.32
C4	0.42, 0.33, 0.25	-0.070	[-0.140, -0.001]	0.035	0.047	4.00
P4	0.50, 0.42, 0.33	-0.067	[-0.130, -0.005]	0.032	0.035	4.51
Pz	0.58, 0.50, 0.33	-0.094	[-0.160, -0.030]	0.033	0.005	8.28

Table S4: Summary of statistics for linear regression models node connectedness (centrality based on the total number of connections), for each oscillation network at 42 and 96 months. Only the statistics for the 'group' parameter are shown, for nodes that were statistically distinct in the 3 groups when adjusted for birth weight or head circumference. Median connectedness values for each group are provided in column 2.

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Node	Median Node Centrality (CAUG, FCG, NIG)	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
Gamma Oscillation Node Strength						
Pz	0.1165, 0.1091, 0.1032	-0.004	[-0.008, -7E-04]	0.002	0.048	3.99
Beta Oscillation Node Strength						
F3	0.1019, 0.1037, 0.1056	0.002	[1E-04, 0.004]	0.001	0.034	4.63

F4	0.1005, 0.1024, 0.1047	0.002	[3E-04, 0.004]	0.001	0.019	5.69
Fz	0.1007, 0.1021, 0.1038	0.001	[1E-04, 0.003]	0.001	0.036	4.51
Pz	0.1122, 0.1106, 0.1084	-0.002	[-0.004, -1E-04]	0.001	0.048	3.99
T7	0.0943, 0.0974, 0.1011	0.003	[0.001, 0.005]	0.001	0.002	10.55
Alpha Oscillation Node Strength						
P4	0.1146, 0.1100, 0.1061	-0.002	[-0.003, -1E-04]	0.001	0.041	4.28
Pz	0.1125, 0.1084, 0.1050	-0.002	[-0.003, -9E-05]	0.001	0.050	3.84
T7	0.1095, 0.1123, 0.1146	0.003	[2E-04, 0.005]	0.001	0.038	4.40
Theta Oscillation Node Strength						
P4	0.1173, 0.1151, 0.1139	-0.002	[-0.003, -4E-04]	0.001	0.012	6.49
T7	0.1067, 0.1104, 0.1143	0.002	[1E-04, 0.004]	0.001	0.040	4.33

Table S5: Summary of statistics for linear regression models node strength (centrality based on the sum of node weights), for each gamma, beta, alpha and theta networks at 96 months. Only the statistics for nodes that were statistically distinct in the 3 groups when adjusted for birth weight or head circumference are shown. Median node strength values for each group are provided in column 2.

Node pair	Regression	Confidence	Standard Error	p-value	Wald statistic
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	Coefficient	Interval (CI)	(SE)		
	Gamma Oscillation Connectivity (Network Edge) Trajectory				
(C3, P3)	-0.016	[-0.030, -0.002]	0.007	0.024	5.13
(P3, Pz)	-0.019	[-0.033, -0.005]	0.007	0.007	7.29
(P3, O2)	-0.012	[-0.023, -0.001]	0.006	0.029	4.80
(P4, O1)	-0.011	[-0.022, -0.001]	0.005	0.032	4.65
(P4, O2)	-0.014	[-0.025, -0.003]	0.006	0.014	6.10
(Pz, O2)	-0.011	[-0.022, -0.001]	0.005	0.031	4.69
	Beta Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.005	[-0.011, -1E-04]	0.003	0.050	3.80
	Alpha Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.006	[-0.011, -0.001]	0.003	0.049	3.90
(P4, O2)	-0.006	[-0.011, -0.001]	0.003	0.05	3.89
	Theta Oscillation Connectivity (Network Edge) Trajectory				
(P3, Pz)	-0.008	[-0.012, -0.002]	0.002	0.015	6.03
(P4, O2)	-0.007	[-0.012, -0.002]	0.002	0.010	6.82

Table S6a: Summary of linear mixed effects regression models statistics for pairwise connectivity trajectories from 42 to 96 months, as a function of time and group, adjusted for birth weight and/or head circumference. Only the statistics for the 'group' parameter are shown, for pairs of nodes for which their connectivity (edge) was statistically distinct in the 3 groups.

Node	Regression Coefficient	Confidence Interval (CI)	Standard Error (SE)	p-value	Wald statistic
Alpha Oscillation Node Connectedness Trajectory					
P4	-0.053	[-0.088, -0.017]	0.018	0.004	8.60
Pz	-0.035	[-0.066, -0.003]	0.016	0.030	4.77
Theta Oscillation Node Connectedness Trajectory					
P4	-0.045	[-0.087, -0.003]	0.021	0.036	4.44
Pz	-0.040	[-0.073, -0.007]	0.017	0.018	5.71

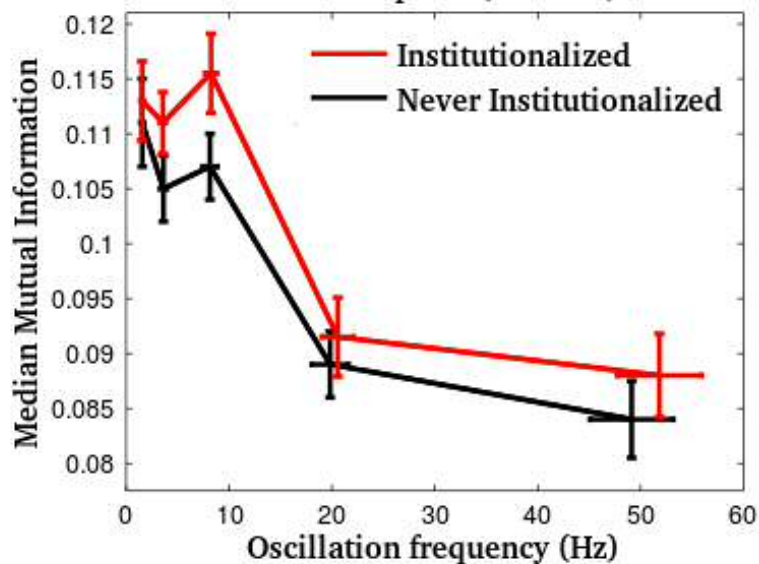
Table S6b: Summary of linear mixed effects regression models statistics for the trajectories of node connectedness from 42 to 96 months, as a function of time and group, adjusted for birth weight and/or head circumference. Only the statistics for the 'group' parameter are shown, for pairs of nodes that were statistically distinct in the 3 groups.

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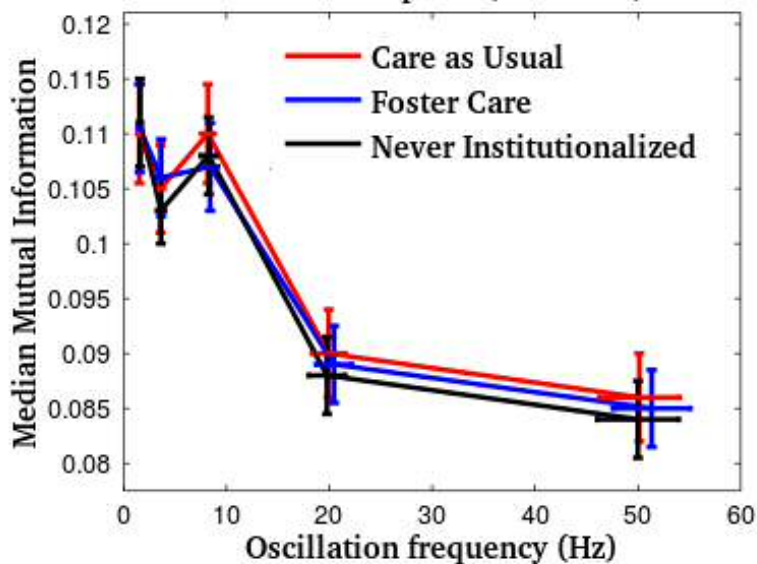
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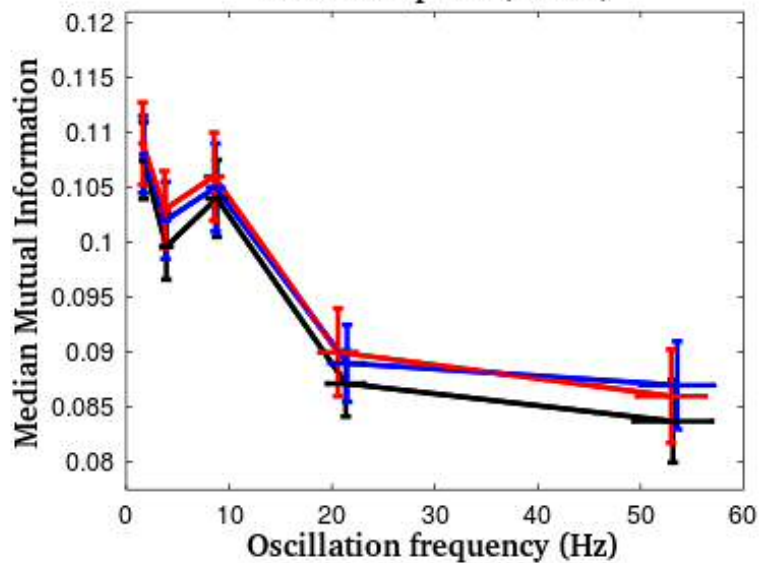
First time point (<30 mo)



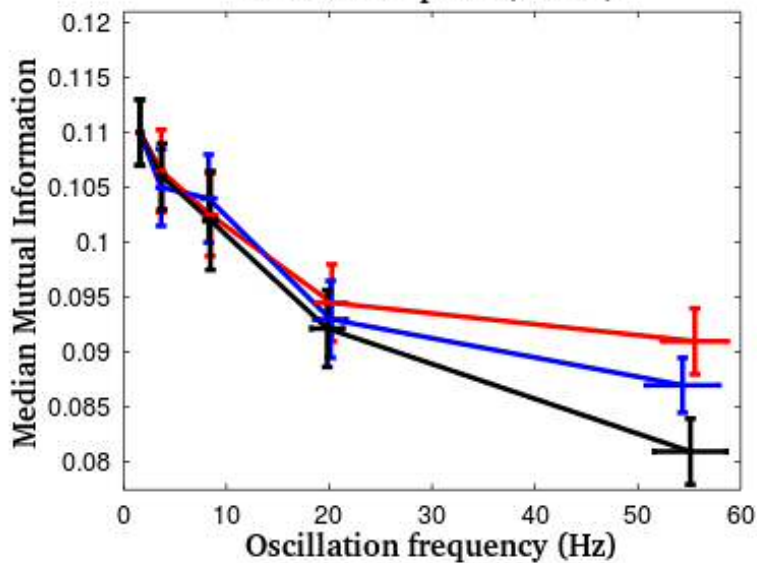
Second time point (30-33 mo)

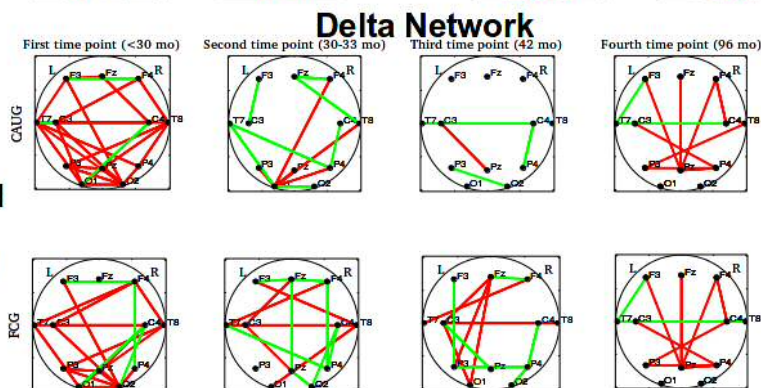
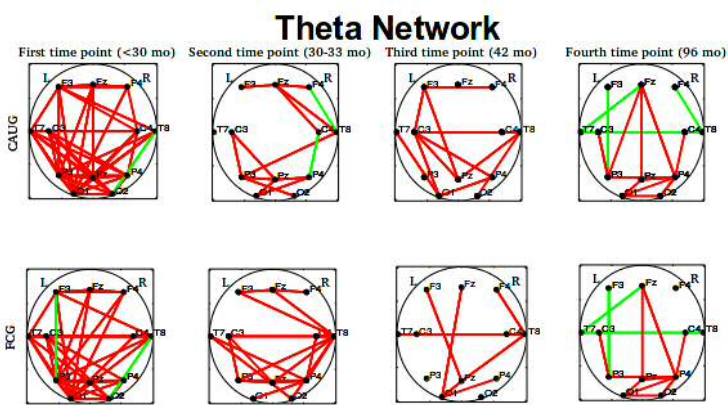
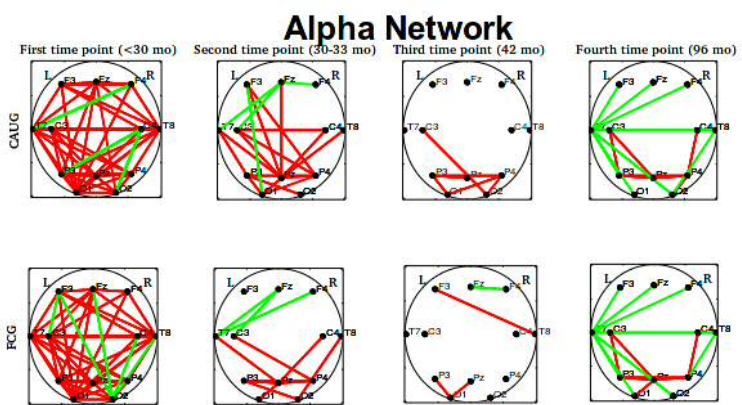
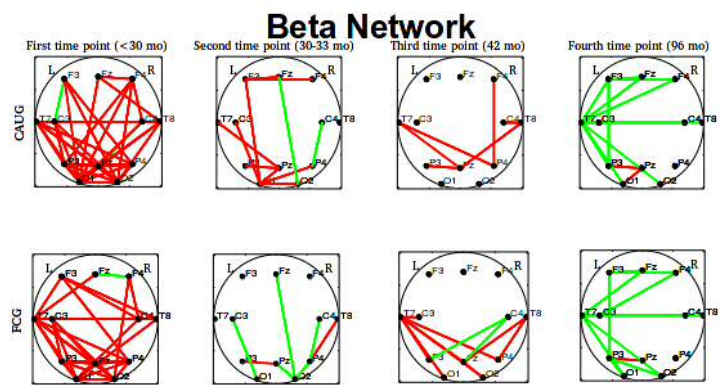
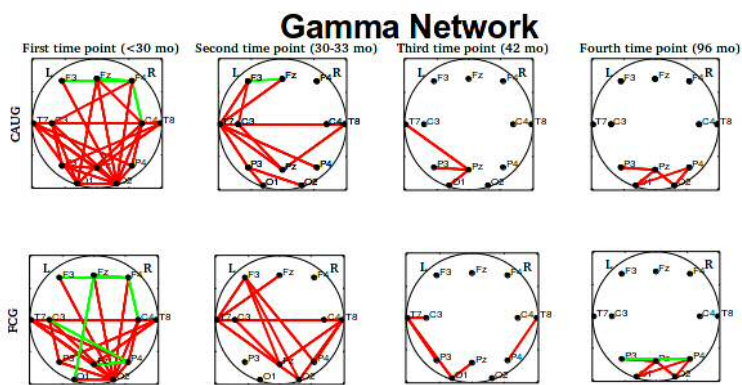


Third time point (42 mo)



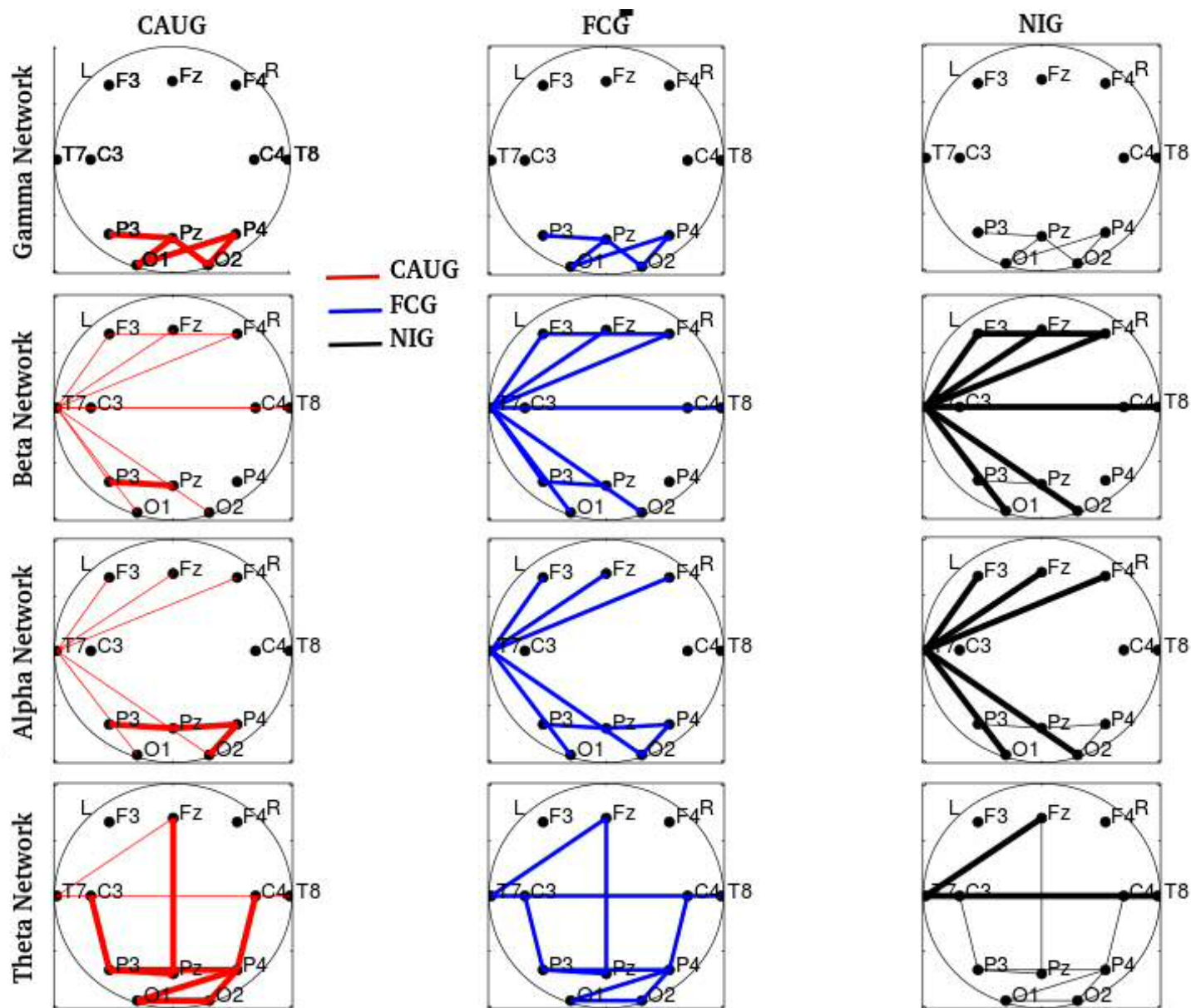
Fourth time point (96 mo)





— Hyper-connected

— Hypo-connected



Highest Aberrant
Node Strength

Lowest Aberrant
Node Strength

